DISORDERS OF THE STRATUM CORNEUM

MEDICAL GRAND ROUNDS

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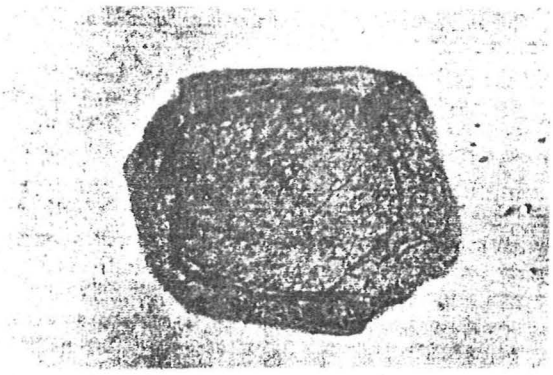
INTRODUCTION

Corneocytes like the one in the first illustration cover the entire skin surface. As an aggregate they form a semipermeable membrane, the stratum corneum, which has a significant impact on systemic homeostasis. It permits man to live with his environment.

This review covers certain aspects of stratum corneum and epidermal function and takes the following form:

1. Anatomy and Embryology
2. An Analogy with the Erythron
3. Cellular Proliferation
4. Percutaneous Penetration
5. Psoriasis
6. Toxic Epidermal Necrolysis
7. Dermatophytosis



ANATOMY AND EMBRYOLOGY

As can be seen in the photomicrograph, corneocytes have no nucleus and are roughly hexagonal in shape (1). They measure about 30 microns in diameter, giving them a surface area of about 1000 square microns (2, 3). Viewed on end they are one-half micron thick (4). Metabolically inactive cells of this sort cover the entire skin surface and as an aggregate have an important influence on the physiologic integrity of the human organism.

Corneocytes which are desquamated from the skin surface are a product of proliferation and maturation within the viable cell layers beneath, and the entire structure as an aggregate comprises the outer portion of the skin or epidermis.

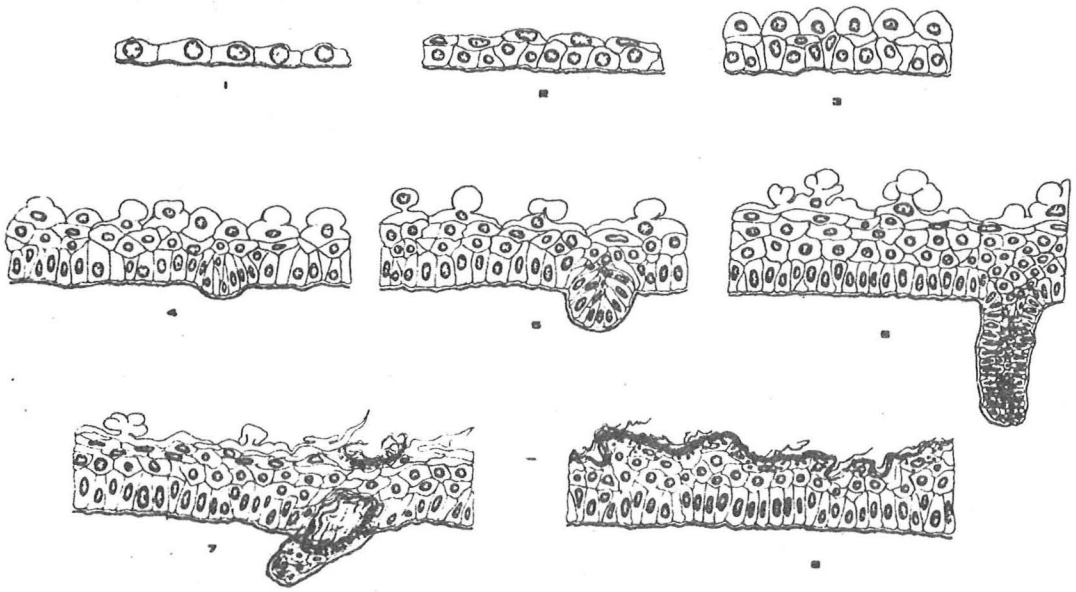
With the light microscope one observes two distinct regions or compartments in the epidermis. Each has contrasting physiologic properties, but it is impossible to discuss each in isolation since their interdependence is so complete. The outer compartment is the aggregate of corneocytes, or stratum corneum, which is today's topic. In certain body regions such as the hands and feet it is highly modified, but throughout the remainder of the skin surface its configuration is relatively uniform.

To maintain the stratum corneum, which is continuously desquamating, there is a steady-state proliferation of keratinocytes. The existence of steady-state proliferation, maturation followed by destruction classifies the epidermis along with the erythron, gastrointestinal epithelium and testis as a tissue of continuous renewal. The functional cells in such tissues are "terminal", because they are a result of prior cell division in a proliferative pool and because they are incapable of further cell division.

Experimental studies of the epidermis are simplified by the homogeneity of its cell populations. We need not concern ourselves with fibroblasts, endothelial cells, connective tissue, or ground substance. Ninety-five percent of the cells are keratinocytes which are bound into a flat syncytium. Other cells of the epidermis, although fewer in number, are equally interesting and they have functions important enough to constitute several future grand rounds. Among the other cells are melanocytes which provide the primary basis of both ultraviolet light exclusion and of racial discrimination. Another cell type, the Langerhans cell, has recently been recognized as important in the development of cutaneous delayed hypersensitivity (5).

Viewed from the skin surface, corneocytes are shed intact, both singly and in small clusters to the outside. This constitutes a continual loss of both protein and lipid to the environment. The magnitude of this loss has been calculated, but it becomes significant only in disease states of excessive desquamation (6). In a normal adult, up to 1.0 gm of corneocytes are desquamated each day, but in states of excessive proliferation such as an exfoliative erythroderma, the rate may increase up to 20 gm/day (7, 6). The size of these aggregates and the rate of their desquamation are of commercial importance to the propietary manufacturers of shampoos and cosmetics, such as Proctor and Gamble. The size of aggregates and the rate of desquamation are also important to investigators concerned with cell to cell interaction since they reflect the adhesive forces which lock these cells together in the first place and since the rate of desquamation is equal to the effective rate of proliferation in the germinative compartment below (8).

Skin is first identified embryologically as two distinct layers at the interface with the yolk sac (9, 10). The outer layer, which is ectodermal in origin, faces into the yolk sac and eventually becomes the epidermis.



Schematic diagram of the 8 stages of periderm development and epidermal differentiation. Corresponding estimated gestation ages for each stage are: (1) <36 days, (2) 35-55 days, (3) 55-75 days, (4) 65-95 days, (5) 85-110 days, (6) 95-120 days, (7) 110-160 days, (8) >160 days.

The inner layer, which is derived from the superficial portion of the mesoderm, becomes the supporting dermis. Throughout fetal development, the epidermis gradually increases in thickness. During much of this time, complete maturation of the keratinocytes does not occur. Even late in the second trimester, the superficial cells at the interface with the amnionic cavity have superficial microvilli. It is felt that these "dynamic" cells account for a significant nutritional uptake into the fetus. At about 160 days of gestation, the stratum corneum develops abruptly. By this time, the epidermis has assumed the form it maintains throughout life. It is bounded on the outside by the environment and on the inside by a basement membrane which is a combined product of keratinocytes and fibroblasts.

Individual keratinocytes are bound to each other by numerous periodic attachment processes or desmosomes (11). It is thought that these structures provide the strength necessary to keep individual keratinocytes attached to each other. Adjacent to the desmosome, cytoplasmic tonofilaments terminate near the surface of the cell, and within the desmosome itself the outer leaflets of adjacent tri-laminar cell membranes fuse to establish a shared portion of cell membrane.

At the inner aspect of the epidermis, the epidermal-dermal junction is composed of four areas (12). The first three are a product of the epidermis: 1) Basal Cell Plasma Membrane: This membrane is irregularly

convoluted, with interdigitating cytoplasmic projections and dermal invaginations. At regular intervals attachment processes occur.

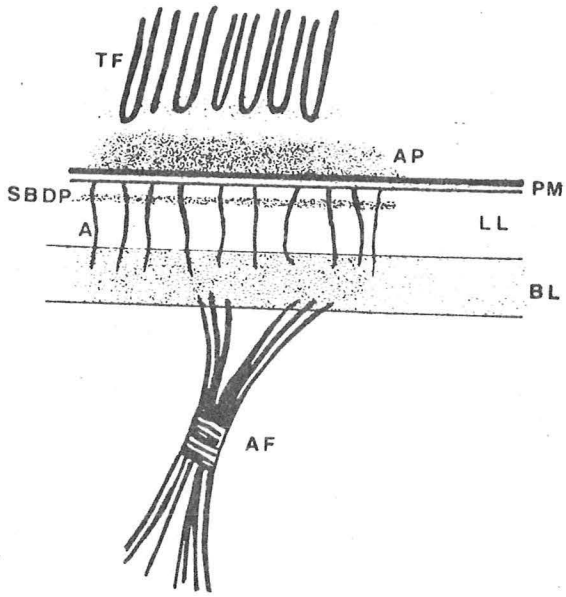


Diagram of hemidesmosome. Tonofilaments (TF). Attachment plaque (AP). Plasma membrane (PM) with a thicker inner leaflet and thinner outer leaflet. Sub-basal dense plaque (SBDP). Lamina lucida (LL). Anchoring filaments (A). Basal lamina (BL) which is more dense beneath the hemidesmosome. Anchoring fibril (AF) showing proximal fanlike fibrous portion which fuses with basal lamina cross-banded mid-zone and distal fibrous portion extending into dermis.

These hemidesmosomes are similar to the "complete" desmosomes which link adjacent keratinocytes to each other. Perpendicular to the hemidesmosome, tonofilaments radiate into the cytoplasm of the cell. It is felt that the strength of this attachment is central in the binding of the epidermis to the dermis. 2) Lamina Lucida: This zone is relatively electron lucent. Beneath the hemidesmosome an electron-dense line, the sub-basal dense plaque may be seen. In the same area fine filaments come through binding the outer leaflet of the basal cell plasma membrane to the basal lamina beneath. 3) The Basal Lamina is a granular appearing electron-dense layer which is also frequently reduplicated. This is felt to be evidence for a continual remodeling of the epidermal-dermal junction. 4) Projecting into the basal lamina one observes dermal fibroma elements, including anchoring fibrils, microfibrils and collagen fibers.

While it has been maintained that skin is the largest body organ, particularly when one attempts to emphasize the importance of one's own specialty, what is not realized is that only a small percentage of the skin forms the membraneous interface. The epidermis as a whole averages 50 microns in thickness and the stratum corneum about 10 microns (13). Calculating for our proverbial 2 square meter man, the volume of the entire epidermis is 100 cubic centimeters, giving it a mass of 100 g while the stratum corneum is 20 cubic centimeters in volume and has a mass of 20 gm.

EPIDERMAL DIMENSIONS

Thickness	50 μm
Area	2.0 m^2
Volume	100 cm^3
Mass	100 g

STRATUM CORNEUM DIMENSIONS

Thickness	10 μm
Area	2.0 m^2
Volume	20 cm^3
Mass	20 g

The volume of the entire stratum corneum approximates that of a small tube of topical steroid.

The relationships may be visualized in another instructive way. The thickness of the stratum corneum approximates that of 10 micron milar recording tape. Its barrier properties and density are also similar. With imagination you may place yourself into a 10 micron polyethylene bag. The bag regenerates from the inside periodically. In the absence of that bag, fluid and microbiologic exchange accelerate causing your death. In an environment of excessive light availability, such as equatorial Africa, genetic selection leads to pigmented milar. This pigment attenuates the ultraviolet light, but not so much that inadequate amounts of vitamin D are formed. If it were not seemingly beneficial for some fraction of the available ultraviolet light to penetrate the epidermis, then all skin might become completely pigmented.

Skin as an Interface

With this as background, it is important to emphasize the concept that skin is an interface. The primary function of the epidermis is to establish and maintain a semipermeable barrier to molecular exchange between the human organism and his environment. The anatomical location of that barrier is the stratum corneum (14, 15). The recognition of the stratum corneum as important in blocking molecular exchange is relatively recent. Before 1945, it was virtually unknown (16, 17, 18, 19). Now, with increasing frequency, the importance of intrusion from the environment is being recognized. Hexachlorophene penetrates intact skin in significant amounts (20, 21, 22, 23) as does gamma benzene hexachloride (Kwell) (24). In some agricultural workers the percutaneous absorption of choline esterase inhibitors must be monitored carefully (25). In contrast, physicians also are interested in increasing the rate that substances penetrate into the skin (26, 27, 28).

It is impossible to describe a wide variety of biological systems in which transport or inhibition of diffusion occurs at an interface. This would include erythrocyte permeability, renal tubular excretion and even molecular transport across mitochondria. Yet, few systems encounter the wide variety of concentration gradients which occur at the skin surface. In a provocative discussion Arndt, et al. discuss the skin as an interface which effectively withstands mechanical, chemical and biologic insults. Furthermore, both thermoregulation and the absorption of ultraviolet light occur at that interface (29).

The gradient of oxygen across the intact stratum corneum illustrates both its barrier properties and its relevance to physiologic processes in the remainder of the skin. It was demonstrated quite early that human skin takes up oxygen from the atmosphere (30). With respect to the stratum corneum, this gas exchange is a passive diffusion process which depends upon concentration gradient across the entire skin. The artificial reduction of the environmental pO_2 decreased the flux of O_2, but the net flux does not reverse until the pO_2 decreases to below 5 mm Hg (31). This means that in normal skin there exists a 155 mm Hg oxygen gradient across the metabolically inactive stratum corneum.

OXYGEN TENSIONS IN NORMAL SKIN

(Evans and Naylor, 1966; Evans and Naylor, 1967)

Location	pO_2 (mmHg)
Stratum Corneum	
Outer Boundary	160
Inner Boundary	5
Viable Epidermis	>5, >50
Dermis	50

Furthermore, the mean pO_2 within the dermis has been determined to be about 50 mm Hg (32). From these data one may conclude that the pO_2 gradient across normal epidermis is from 50 to 5 mm Hg. Whether the majority of viable keratinocytes are exposed to a partial pressure near 5 or near 50 is not known, but the possibility exists that alterations in the partial pressures of oxygen as well as carbon dioxide may be partially responsible for the terminal maturation of keratinocytes.

Parenthetically, keratinocytes have been studied for various additional physiological immunological, and biochemical reasons. Epidermal volume, cellular proliferation rates, and transit times have been modeled as a negative feed-back system and work with chalones was initiated with the epidermis (33). Phagocytosis of foreign material by keratinocytes has been observed (34). Within the epidermis there is both a partial shunt reutilization of DNA precursors (35) and a simultaneous release of DNA to the dermis. This release of partially catabolized DNA into the dermis is fundamental to the genesis of the deposition of antinuclear antibodies in the epidermal basement membrane of patients with lupus erythematosus (36). And finally, systemic metabolic diseases are reflected in the epidermis (37, 38).

THE ERYTHRON-KERATON ANALOGY

The best way to illustrate epidermal structure and function is to establish an analogy with a more familiar tissue. It is instructive to assess the similarities and differences between erythrocytes and corneocytes. We might call it the Erythron-Keraton analogy.

Definitions

Erythron: The combined mass of immature and mature erythrocytes

Keraton: The combined mass of immature and mature keratinocytes

At first erythrocytes and keratinocytes may seem unlikely candidates for an analysis by analogy. In fact, these two tissues have similar cellular processes, extending from proliferation to destruction. An interesting aspect is that cellular proliferation in these tissues has been studied with different techniques and from different points of view. Furthermore, medical education pays considerable attention to the erythron and virtually no attention to the epidermis. Both cell lines accumulate a specialized protein in large quantity. In the erythrocyte it is hemoglobulin, and in the keratinocyte it is keratin. In the final stage of erythrocyte maturation extrusion of the nucleus occurs, leaving a functional cell which is incapable of mitosis, and is incapable of regenerating gene products. In the epidermis, dissolution of the nuclear contents occurs abruptly as a final step in maturation (39, 40, 41).

With respect to function major differences between two tissues are apparent. Erythrocytes facilitate gaseous exchange between pulmonary alveoli and tissue. Corneocytes inhibit percutaneous molecular exchange. Other major differences limit the applicability of this analogy, but it does allow one to conceptualize the epidermis more clearly. Because of this, the analogy will serve as a background for the remainder of the discussion.

CELLULAR PROLIFERATION IN THE EPIDERMIS

The function of keratinocytes is to maintain a semipermeable membrane at the skin surface. Since continual desquamation of mature keratinocytes (corneocytes) occurs at the skin surface, cell division in the proliferative portion of the epidermis must replace that loss.

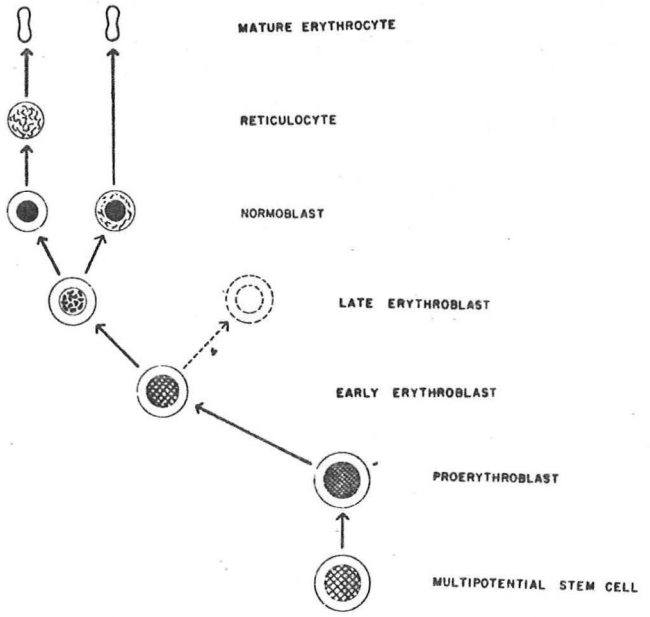
One may determine the rate of cellular proliferation by compartmental analysis for both the epidermis and the erythron. Physiologically, one can identify three compartments: proliferation, maturation and function. These compartments are more easily visualized as such for the erythron since the first two are physically removed from the latter, whereas in the epidermis all three are adjacent. The locations of epidermal and erythron compartments are contrasted in the table. In both tissues the proliferative cells and maturing cells are morphologically indistinguishable from each other.

COMPARTMENT	ERYTHRON	KERATON
Proliferation	Bone Marrow	Stratum Germinatium
Maturation	Bone Marrow	Stratum Spinosum
Function	Vascular Space	Stratum Corneum

The proliferation and maturation of erythrocytes from the multipotential stem cell has been examined closely with microscopic techniques. This diagram for the erythron is modified from Harris' monograph and illustrates the maturation of erythrocytes through the preerythroblast, early and late erythroblasts, normoblast, reticulocyte and eventual mature and functional erythrocyte (42). The erythrocyte, by definition a terminal cell, is incapable of cell division. It is also the functional cell.

PHYSIOLOGIC PROCESSES

	Erythron	Keraton
Proliferation:	Bone marrow	Nucleated keratinocyte compartment



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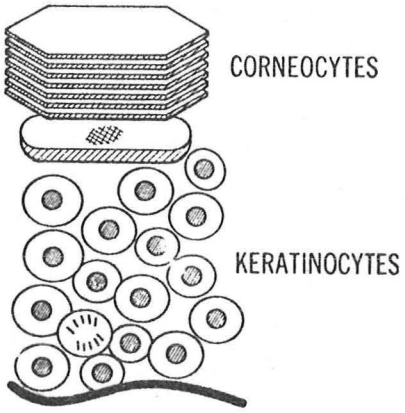


Maturation:	Accumulation of hemoglobin	Accumulation of keratin
	Loss of mitotic capacity	Loss of mitotic capacity
	Decrease in volume	Increase in volume
	Nuclear extrusion	Nuclear dissolution
Function:	Oxygen and carbon dioxide transport between pulmonary alveoli and tissue.	Inhibition of percutaneous molecular exchange.
Measures of Integrity:	Hemoglobin concentration per peripheral vascular volume	Percutaneous penetration of identifiable molecules.

Within the epidermis a similar process occurs. Stem cells have not been identified morphologically, but studies of regeneration and repopulation have demonstrated their existence. Subsequent to a series of cell divisions, a selected fraction of the cells differentiate into metabolically inactive but physiologically functional aggregates of corneocytes.

The rate of cellular proliferation within the erythron has been examined from two vantage points. In compartmental analysis, one identifies the separate compartments, counts the number of cells within each compartment, and determines the mean time during which a cell resides in that compartment or functional state. With this data one determines the rate of cellular proliferation and of cellular destruction. This was accomplished relatively early for the erythron since the functional compartment was easily identified as the peripheral vascular space, and since it was observed that normal erythrocytes remained in that space for a constant time of 120 days. From this the rate of destruction and obligate rate of effective production were determined quite accurately. The data are summarized in the table (42).

	Cells/kg. ($\times 10^9$)	Relative Number	Turnover Time (Days)
Marrow			
Nucleated	5.0	1.5	1.7
Reticulocytes	5.0	1.5	1.7
Circulation			
Reticulocytes	3.3	1.0	1.2
Adult Erythrocytes	330.0	100.0	120.0

Distribution of the erythron
(Harris and Kellermeyer, 1970

Knowing that there were 330 x 10^9 RBC/kg and that the time of survival within the peripheral vascular space before senisence was 120 days, it was calculated that rate of effective erythrocytes production

was the compartment size divided by the time in the compartment or (330/120) x 10^9 RBC/kg/day or 2.75 x 10^9 RBC/kg/day. For a seventy kilogram man this represented 180 x 10^9 RBC/day. From these data the mean duration of cells within the bone marrow was calculated. Since the number of erythrocyte precursors represented 3.3% of the functional compartment, they resided in the combined proliferative and maturation compartment for 3.3% of the time or four days.

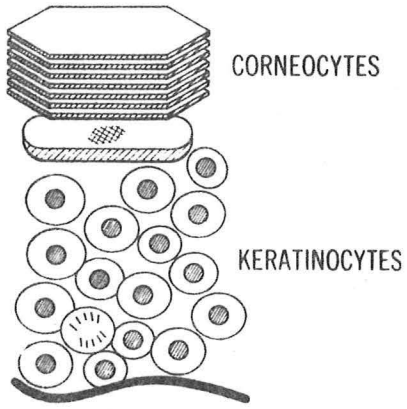
COMPARTMENTAL ANALYSIS

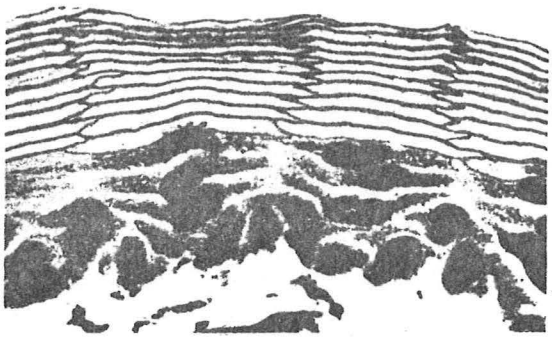
Compartment Size	Erythron (Cells/70 kg.)	Keraton (Cells/$2m^2$)
Proliferation and Maturation	7 x 10^{11}	1 x 10^{11}
Function	230 x 10^{11}	0.4 x 10^{11}

COMPARTMENTAL ANALYSIS

Turnover Time (Days)	Erythron	Keraton
Proliferation and Maturation	4	31
Function	120	14
Total	124	45
Production Rate (Cells/Day)	1.8 x 10^{11}	2.9 x 10^9

Compartmental analysis has only recently been applied to normal human skin (43). The figure illustrates a model of the skin with corneocytes stacked individually on each other. This phenomena of stacking may in fact occur as it has been observed in several animals and has been reported occasionally in humans (44, 45, 46, 47, 48). From the model it is obvious that the progression of rigid corneocytes through this is linear (49, 50).





Frozen section of hamster epidermis stained with methylene blue and expanded at pH 12. Beneath the regularly aligned and interdigitating cells of the stratum corneum are 3 to 4 layers of aligned nucleated cells. A number of smaller unflattened basal cells lie beneath each column. [Scale = 30 μm]

(MacKenzie, 1975)

Furthermore, the number of cell layers within the epidermis is relatively constant, with a mean of about 20 (51, 52). It has been determined with both fluorescent stains and radioactive tracers that the mean turnover time of the entire epidermis is about 14 days (53, 54). Therefore, one may calculate that in the steady state, 20/14 or 1.4 cell layers desquamate each day from the surface.

To determine how many individual cells this rate of desquamation and proliferation represents one must determine the surface density of two compartments: proliferation/maturation and function. Surface area determination for individual corneocytes have been made. It was found that corneocytes in normal human skin were relatively constant in their surface area, measuring about 1000 μ^2 (55, 3). Given that there are 20 cell layers, the surface density of corneocytes is 20 per 1000 μ^2 or $2 \times 10^4/mm^2$ which is a more useful dimension. In an independent study the surface density of nucleated epidermal cells was determined to be $5 \times 10^4/mm^2$ (13). With this data, it is possible to determine the absolute proliferation rate and turnover time of cells in the nucleated (proliferation/maturation) compartment. The absolute desquamation rate is 1.4×10^3 cells/day/mm^2 or 2.9×10^9 cells/day/$2m^2$. The turnover time of nucleated compartment was determined to be 31 days, making the total epidermal turnover time 45 days.

Summary of turnover time calculations. Rates pertain to the two compartments under one surface corneocyte

Parameter		Value
T_c	Turnover time (corneocyte compartment)	14 days
N_c	Cell layers (corneocyte compartment)	20 cell layers
r_1	Turnover rate (corneocyte compartment) (N_c/T_c)	1·4 cell layers/day
A	Surface area (one corneocyte)	$9{\cdot}4 \times 10^{-4} mm^2$
N	Keratinocytes per mm^2	$4{\cdot}7 \times 10^4/mm^2$
N_k	Keratinocytes per corneocyte area ($A \times N$)	44 cells/corneocyte area
$r_2 = r_1$	Rate of maturation and loss from the keratinocyte compartment	1·4 cells/day/corneocyte area
T_k	Turnover time (keratinocyte compartment (N_k/r)	31 days
T_e	Epidermal turnover time (T_c+T_k)	45 days

The second method for determining cellular proliferation and maturation has been with the use of radioactive tracers which are incorporated quantitatively into cell constituents, particularly the incorporation of tritium labeled thymidine into DNA (56, 57, 58). It is of interest that this more recent method confirmed to the hematologist that traditional compartmental studies were realistic, while for the dermatologist the model based on functional compartment depletion was developed after the tracer techniques. Compartmental analysis has in turn confirmed the more elaborate tracer technique.

CLINICAL DISORDERS

The erythron-keraton analogy may be extended to certain clinical disorders and I shall consider several of them in some depth. Looking at these tissues by compartments, one might hypothesize disorders to occur in each. This does in fact happen. By the repetitive application and removal of cellophane tape one may deplete the stratum corneum of its entire complement of corneocytes. This obviously takes more than twenty consecutive applications and when completed, the area becomes red and tender. This is analogous to hemorrhage for the erythron, and both might be described as acute functional compartment depletion. Dermatophyte infections are limited to the stratum corneum, but the presence of such an infection causes a significant alteration in the barrier properties of the stratum corneum. This disorder is analogous to erythrocyte infestation with malarial parasites.

ERYTHRON-KERATON ANALOGY

Disorder	Erythron	Keraton
Functional Compartment		
Depletion	Hemorrhage	Tape Stripping
Infection	Malaria	Dermatophytosis
Proliferative Compartment		
Benign Hyperproliferation	Polycythemia Vera	Psoriasis
Necrosis	Aplastic Anemia	T.E.N.

The analogy is equally informative in illuminating disorders of the lower compartment. Psoriasis may be defined as an idiopathic benign hyperproliferative dysfunction of the epidermis. Polycythemia vera may be defined in the same terms. Also, acute necrosis of the proliferative and maturation compartments has important implications for a patient. Toxic epidermal necrolysis, when caused by drug reactions, involves the acute death of the entire viable epidermis. Because the turnover time of the functional compartment of the epidermis is more rapid than that of the erythron and since the stratum corneum is dependent upon the physical integrity of the viable epidermis beneath, toxic epidermal necrolysis is a much more rapidly developing disorder than is aplastic anemia.

STRATUM CORNEUM STRIPPING AND EPIDERMAL PROLIFERATION

The process of removing successive layers of the stratum corneum with cellophane tape stripping and thereby of increasing the rate of mitosis in the underlying keratinocytes was first introduced in 1951 by Pinkus (59, 60). Cellophane stripping was central to the early experimental literature on epidermal barrier function and the effects of stripping have been studied in a variety of systems. Since the barrier to percutaneous chemical exchange is the stratum corneum, stripping reduces that barrier and increases percutaneous penetration (61, 62). Skin stripping has also been used to stimulate keratinocyte proliferation in biochemical studies (63).

At a physiological level, the removal of the stratum corneum exposes underlying viable cells to the external environment. To illustrate one aspect of the barrier function of the stratum corneum, cellophane tape stripped and normal rat skin were both covered with wet dressings containing aqueous 0.5% silver nitrate solution. For many years silver nitrate in this concentration was standard treatment for extensive thermal burns. In the area covered by intact stratum corneum the nucleated portion of the epidermis was morphologically normal. In areas denuded of the stratum corneum nuclei were crenated and the cytoplasm was eosinophilic. Those observations were reliable evidence of a severe toxic insult to the epidermis. The stratum corneum protects the viability of the nucleated portion of the epidermis itself from environmental assault.

Since the effect of cellophane stripping on the keraton may be considered analogous to the effect of hemorrhage on the erythron, it is instructive to assess the response to the artificial replacement of the missing stratum corneum. Fisher and Maibach stripped skin and observed nearly a ten-fold increase in mitotic index which is a reliable correlate of the proliferation rate. Occlusion with a polyethylene membrane blunted the mitotic response to a two-fold increase (64). This is equivalent to the same blunting which one observes if hemorrhage is treated with transfusion.

MITOTIC INDEX (%)

Normal Skin	
Control	0.65 ± 0.08
Occluded	0.65 ± 0.07
Stripped Skin	
Control	5.15 ± 0.78
Occluded	1.04 ± 0.16

Effect of occlusion on mitotic rates in normal and stripped skin (Fisher and Maibach, 1972)

It is clear from these data that a negative feedback mechanism which recognizes the absence of stratum corneum and that this recognition is aborted by the presence of polyethylene film.

To assess the barrier properties of intact stratum corneum, Stoughton applied six unrelated compounds to both stripped and intact human skin (62). For each compound a clinical effect could be observed. The decrease in concentration required to elicit each effect in the absence of the stratum corneum was between four and five magnitudes.

EFFECT OF PHARMACOLOGICAL AGENTS TOPICALLY APPLIED TO NORMAL AND STRIPPED HUMAN SKIN

Agent	Minimum Concentration Giving Biologic Reaction	
	Stripped	Unstripped
Privine	10^{-6}	10^{-1}
Otravine	10^{-6}	10^{-1}
Hypertension	10^{-5}	10^{-1}
Histamine HCl	10^{-6}	10^{-1}
Flucinolone acetonide	10^{-7}	10^{-3}
Betamethasone-17-valerate	10^{-7}	10^{-3}

(Stoughton, 1972)

Furthermore, the concentration required to elicit the biologic effect in stripped skin was one of the same order of magnitude required by injection.

EFFECT OF PHARMACOLOGIC AGENTS INJECTED INTRADERMALLY INTO NORMAL HUMAN SKIN

Agent	Minimum Concentration Given Biologic Reaction (0.05cc)
Privine	10^{-6}
Otravine	10^{-6}
Hypertension	10^{-6}
Histamine HCl	10^{-6}
Fluocinolone acetonide	10^{-7}
Betamethasone-17-valorate	10^{-7}

(Stoughton, 1972)

PERCUTANEOUS PENETRATION

Case 1

Case 1 is an eleven year old girl who developed blisters, generalized erythroderma, and exfoliation within the first 24 hours of life (65). A diagnosis of epidermolytic hyperkeratosis was made at that time and her subsequent course was consistent with that diagnosis. Medical care for her skin during the next eleven years consisted of topical compresses, emollients and keratolytics. She also received intermittent systemic antibiotics and vitamins. She did not receive topical or systemic corticosteroids. In July, 1971, she was started on an experimental comparative protocol which included topical 0.05% triamcinolone acetonide cream to half of her skin surface, t.i.d., without occlusion. Four weeks later her facial features appeared cushingoid. The patient's adrenal function was evaluated at that time, and the table lists her plasma and 24 hour urine values. In August, after one month of intensive topical steroid use, her adheral function was clearly suppressed. By November, three months after discontinuing the treatment, her values had returned to the normal range. It is of interest that the investigators repeated the trial with the same results several months later.

DATE	PLASMA CORTISOL AM (5-28mg/dl)	PLASMA CORTISOL PM (5-18mg/dl)	TWENTY-FOUR HOUR STEROIDS 17-KETO- (4-15mg)	TWENTY-FOUR HOUR STEROIDS 17-HYDROXY- (2-10mg)
August 4	2	1	3.2	0.44
November 5	11	6	18.4	4.7

Adrenal function before and after discontinuing topical triamcinolone acetonide 0.05% cream

(Schorr and Papa, 1973)

The repetetive application of a potent fluorinated steroid induced an almost complete adrenal suppression and cushingoid facial features within a relatively brief period of time when the drug was applied to skin with decreased barrier function. The histopathology of the defect in epidermolytic hyperkeratosis allows one to predict such an occurrence. The stratum corneum is completely disrupted in this condition.

What is to be learned from this study is that the application of potentially toxic chemicals to damaged epidermis must be done with thought and with care.

Damage to the stratum corneum has also been used clinically by the pharmaceutical industry to enhance percutaneous penetration of biologically active molecules. As is well known, a number of dermatoses such as psoriasis, atopic dermatitis, chronic contact dermatitis and pretibial myxedema are steroid responsive. An important consideration in the formulation of preparations which deliver the steroid to the skin in sufficient amounts is the barrier effect of the epidermis. Sodium lauryl sulfate, an emulsifier, is known to denature protein, and in particular to increase the rate of penetration of other molecules. We treated a group of patients with a non-fluoronated corticosteroid combined by the drug manufacturer with 0.5% sodium lauryl sulfate (66). The emulsifier was present in a concentration high enough to damage the stratum corneum, and high enough to cause an additional primary irritant dermatitis to several of the patients. In this instance, the drug formulation backfired. We validated the observation by producing a similar dermatitis in normal control subjects, and the preparation was withdrawn from study (66).

One clinical lesson derived from this is that skin once damaged by an earlier insult may be more easily damaged by what might otherwise be a trivial insult (67, 68). A continuing cycle of dermatitis and abnormal barrier generation ensues. Since it is the tendency of patients

and potential patients to wash their skin eruptions, a positive feedback system of uncontrolled washing frequently ensues. With this in mind the duty of the physician may be simple -- that of stopping all treatments, applications and washes.

On a scientific level several factors have been shown to be important in the rate of penetration of chemical substances into the skin (69). These are summarized in the table. Much of this work has been accomplished by three groups of investigators: Blank and Sheuplein in Boston, Stoughton in San Diego, and Maibach in San Francisco.

FACTORS INFLUENCING PERCUTANEOUS ABSORPTION

1. Humidity
2. Temperature
3. Vehicle
4. Dermal Circulation
5. Thickness of Stratum Corneum
6. Anatomic Location
7. Disease States

The next few tables illustrate some of these factors and they are taken from Stoughton (62).

The data in the first table illustrate the effect of high humidity on the penetration of commonly used topical steroids: triamcinolone acetonide (Kenalog/Aristocort), fluocinolone acetonide (Synalar), and hydrocortisone, which is known by a myriad of names. For each of the three there was a ten-fold increase in the amount of drug which penetrated. This has profound implications for those of us who wish to enhance the amount of a drug which penetrates into the skin.

INFLUENCE OF HUMIDITY ON PERCUTANEOUS ABSORPTION
OF THREE GLUCOCORTICOSTEROIDS IN HUMAN SKIN IN VITRO

Agent	Percent Penetration at 20 Hours	
	50% Humidity	100% Humidity
Triamcinolone acetonide	0.21	2.05
Fluocinolone acetonide	0.16	1.76
Hydrocortisone	0.12	1.41

(Stoughton, 1972)

Likewise the ambient temperature of the environment has been shown to influence the rate of penetration of the same therapeutic substances into the skin, producing a four-fold increase.

INFLUENCE OF TEMPERATURE ON PERCUTANEOUS ABSORPTION
OF THREE GLUCOCORTICOSTEROIDS IN HUMAN SKIN IN VIVO

	Percent Penetration at 20 Hours	
	10° C	37° C
Triamcinolone acetonide	0.08	0.35
Fluocinolone acetonide	0.12	0.41
Hydrocortisone	0.16	0.38

(Stoughton, 1972)

More recently it has become increasingly apparent that the material in which a substance is suspended or dissolved will influence the penetration of substance into the skin (70, 71, 51). I show here the results on one study illustrating the penetration of an important antifungal and antiparasitic agent, thiabendazole from three different bases. Hydrophilic ointment was used for many years as a base for topical applications. It is perfectly clear that it retarded the rate of penetration when compared to both the gel and dimethylacetamide. The influence of the base stems from several factors. If the biologically active substance is more soluble in the base than in the stratum corneum, then the partition coefficient will be in the direction of staying in the vehicle. Secondly, those bases which have second ingredients which damage the stratum corneum will enhance penetration. Finally, occlusive bases tend to enhance penetration.

IN VITRO PENETRATION OF ^{14}C THIABENDAZOLE

	Percent Penetration at 20 Hours	
	Human Leg Skin	Mouse Skin
Dimethylacetamide	9.4	14.6
Gel	0.7	1.3
USP Hydrophilic ointment	0.1	0.3

(Stoughton, 1972)

Finally, those bases having second ingredients which alter any of the other named factors will also by definition increase the rate of penetration. From this one may generalize a rule by which the same ingredient in several different topical skin preparations may be compared.

GEL > OINTMENT >> CREAM

Perhaps the most important intervention is the use of polyethylene occlusion over the area to which a topical drug has been applied. This simple maneuver enhances penetration in some assay by two magnitudes. Occlusion increases both the temperature and the humidity and it establishes a reservoir of active medication which is not rubbed off. This explains why occlusive therapy is so popular among those who treat skin disorders (72).

EFFECT OF OCCLUSION ON PERCUTANEOUS PENETRATION

Agent	Minimum Concentration to Produce Blanching	
	No occlusion	Occlusion
Triamcinolone acetonide	10^{-4}	10^{-6}
Fluocinolone acetonide	10^{-4}	10^{-6}
Hydrocortisone	10^{-2}	10^{-4}

(Stoughton, 1972)

PSORIASIS

Psoriasis is an important disease for those who concern themselves with the epidermis. It is common, frequently disfiguring, occasionally disabling, and rarely fatal. The investigation of its cause(s) now occupies the attention of biochemists, immunologists and geneticists. No animal models exist.

The primary lesion of psoriasis is a small papule with superficial scale. Such papules may enlarge and coalesce into well demarcated plaques involving large areas of skin. Viewed from the outside one sees white scale. This result of light refraction (scattering) as light passes through structures of continuously changing refractive indices and through a structure which is excessively thick.

Histologically one observes: 1) elongation and edema of the dermal papillae, 2) elongation of the nucleated portion of the epidermis (acanthosis), 3) relative thinning of the suprapapillary portions of the epidermis, 4) thickening of the stratum corneum with retained nuclei (hyperkeratosis with parakeratosis), and 5) the presence of neutrophils within the epidermis (microabscesses) (73).

Both psoriasis and polycythemia vera are more easily visualized when their definitions are compared. Psoriasis is an idiopathic hyperproliferative disorder of the epidermis characterized by the excessive release of corneocytes to the stratum corneum. Nucleated cells are seen frequently indicating a premature release from the maturation compartment. The proliferative and maturation compartments are vastly hyperproliferative,

increasing many times in size. Each corneocyte may function normally, but as an aggregate their barrier function is faulty. Treatment consists of the removal of corneocytes with keratolytics and inhibition of cell division with chemotherapy and ultraviolet light.

Polycythemia vera may be defined as an idiopathic hyperproliferative disorder of the erythron. It results in a sustained elevation of the hematocrit, hemoglobin and red cell count. The total red cell volume may range up to three times normal. Reticulocytosis is present and occasionally nucleated erythrocytes may be seen, indicating a premature release from the bone marrow. The bone marrow itself is vastly hyperproliferative, replacing much of the yellow fatty marrow. The erythrocytes which are produced function relatively normally, but as an aggregate they may cause vascular insufficiency. Treatment consists of the removal of erythrocytes by venesection and inhibition of cell division with chemotherapy. Although this analogy breaks down when carried much further, it does provide an interesting perspective for visualizing both diseases.

Another way to model psoriasis is as a process of incomplete or abnormal stratum corneum production. The corneocytes produced in the lesion of psoriasis and the barrier function of the aggregate of cells is clearly abnormal. This model, although certainly incomplete and perhaps incorrect, may be used to rationalize several observations.

In a variety of systems, including transmembrane water penetration it has been shown that the stratum corneum barrier is defective in psoriasis (74, 75, 76). Taylor and Halprin observed greater than fifty percent uptake of salicylic acid applied under occlusion to the skin of patients with psoriasis (77).

Baxter and Stoughton (78) in addition to others (64, 79) have observed a significant decrease in mitotic index of psoriatic skin treated with occlusion alone. This means that the artificial replacement of the defective stratum corneum barrier is associated with the return in

MITOTIC INDEX IN PSORIATIC SKIN TREATED WITH OCCLUSION

(Baxter and Stoughton, 1970)

Type of Occlusion	Mitotic Index (Percent)
None	1.97
Plastic	1.30
Plastic + Corticosteroid	0.32

[N=9; $P < 0.01$ for all differences]

the rate of cellular proliferation toward normal. It is of interest that this observation is similar to the blunting of the mitotic response to cellophane tape stripping by plastic occlusion.

An observation which is contradictory to this model in certain respects is that acute guttate psoriasis develops seemingly before stratum corneum damage occurs. This does not invalidate the model as a possible explanation for the persistence of psoriatic lesions after the acute inciting event such as a hemolytic streptococcal pharyngitis has subsided.

TOXIC EPIDERMAL NECROLYSIS

Massive epidermal necrosis may occur from any one of several insults. Burns, which are a direct physical destruction caused by flame and heat, may cause signific homeostatic complications. Despite continuing progress in burn care, the mortality rate for third degree burns of fifty percent of the body remains at about fifty percent. A less common disorder, toxic epidermal necrolysis results from a relatively specific immunologic destruction of the epidermis. It illustrates the absolute requirement for an intact skin barrier to maintain life (80). A similar but more superficial and thus more benign process results from a similar insult to the epidermis caused by a toxin produced by several type specific staphylococci (81, 82, 83).

Case 2

A 64 year old white woman with numerous large blisters was admitted to Jackson Memorial Hospital in Miami in 1972 (84). Three weeks before admission her home was fumigated with a mixture containing acrylonitrile and carbon tetrachloride. One day before admission she developed a pruritic eruption on her abdomen and blisters on the soles of her feet. At the time of admission, 90% of her skin was covered with bright erythema and blisters. She was febrile and disoriented. A diagnosis of toxic epidermal necrolysis (T.E.N.) was made on clinical grounds, and she was admitted to the burn unit to be treated in the same manner as patients with widespread burns. A skin biopsy showed changes typical of toxic epidermal necrolysis. The entire epidermis was necrotic and separated from the dermis. A sparce infiltrate of lymphocytes and histiocytes surrounded the dilated blood vessels of an edematous papillary dermis. She was treated with systemic fluids and electrolytes, antibiotics and adrenocorticosteroids. Subsequently, she developed septic shock and gastrointestinal hemorrhage. She died two days after admission.

The patient was one of four, each of whom developed acute fulminant toxic epidermal necrolysis three weeks after exposure to the same fumigant. Relatives of each patient received the same exposure without noticeable effect. Both the time course and the sporatic incidence were consistent with a drug reaction as opposed to a direct toxic affect to the epidermis. In each, the initial pathology was limited to the skin, primarily the epidermis where there was complete necrosis. Three of the four patients died despite intensive support.

Toxic epidermal necrolysis as a disease illustrates some of the differences between the epidermis and the erythron. Aplastic anemia in the absence of hemolysis has a relatively delayed impact since the rate of mature erythrocyte destruction is less than one percent per day. Furthermore, the physical separation of the functional cells from the proliferative compartment means that there is no structural dependence. In contrast, the complete compartment renewal time is 14 days for the stratum corneum. This patient illustrated that the stratum corneum depends upon the integrity of the inner cells for its anchoring to the patient. With the destruction of the maturing keratinocytes, there was a complete loss of structural integrity. Blisters formed leaving the patient's dermis exposed, and she died within two days.

The erythron is also different in another respect. The medical science of giving transfusions is farther advanced than that of artificial skin replacement. This may not be indefinitely the case with the availability of homografts and xenografts for the treatment of burn victims and with the recent successful tissue culturing of keratinocytes (85).

DERMATOPHYTOSIS

The dermatophytes are a group of related fungi with an affinity for cornified epidermis. They affect man with a worldwide distribution (35).

The restriction of dermatophyte infection to the stratum corneum is the result of the growth inhibitory effect of a serum factor, most likely transferrin (87, 88, 89). In tissue culture whole skin does not inhibit the penetration of dermatophytes into the viable portion of the skin. These observations are consistent with the current assumption that molecules as large as transferrin (Mw = 85,000) diffuse readily across the basement membrane into the extra-cellular space of the epidermis. Furthermore, it is consistent with the assumption that the first significant block to molecular diffusion occurs at the innermost

level stratum corneum, since dermatophyte hyphae frequently are found throughout that structure.

Dermatophyte infections are analogous to the infection of mature erythrocytes with malaria. Both severely alter the functional characteristics of the host cell and both cause its premature destruction. Data from a study by Berk, et al. are included in the table (90). It is seen that a reactive hyperproliferation occurs in the proliferative compartment of the epidermis.

MEAN EPIDERMAL LABELING INDEX IN DERMATOPHYTOSIS

(Berk, Penneys, Weinstein, 1976)

Skin Site	Labeling Index (Percent)
Control	2.7
Dermatophyte	12.2

O'Quinn, et al. investigated the types of skin disorders which caused patients to have significant employment and school attendance problems (91). The majority of patients had one of four disorders: contact dermatitis, atopic dermatitis, psoriasis, and discoid lupus erythematosus. In each of the first three disorders, there is both a defect in the generation of the stratum corneum and stratum corneum barrier properties which significantly compromised. In view of this it is clear that disorders of barrier function are a common accompanyment in skin disease.

I hope this discussion has illustrated to you why I visualize the epidermis, with its stratum corneum, as being somewhat like Indianapolis. Almost everyone goes through it at one time or another, but no one ever seems to stop there. Next time you have an opportunity to look through the epidermis, be aware that the structure you are looking through also has important physiologic function.

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